REMARKS

I. Preliminary remarks

Upon entry of the instant amendment, claim 31 has been amended to recite "wherein the non-Aβ polypeptide is for treatment of a human patient that has been diagnosed with a CNS disorder." Support for this amendment can be found, for example, at page 3, lines 15-26. No new matter has been added.

II. The rejection under 35 U.S.C. § 112, second paragraph, is moot and should be withdrawn.

The examiner rejected claims 69-77 as being indefinite because the recitation of "an human amyloid beta (Aβ) polypeptide" is ambiguous. This rejection is moot because the term "human" has been deleted from independent claims 69, 70 and 72.

III. The rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

The examiner rejected claims 31, 33-46, 48 and 68 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The examiner acknowledged that the application teaches how to use the claimed composition for treating Alzheimer's disease but asserted that it fails to provide any further guidance for treating any CNS disorder. Applicants disagree.

The basis of applicants' invention is the transport of therapeutic agents across the blood brain barrier (BBB), not the provision of novel treatments for CNS disorders. A variety of known therapeutic agents for diverse CNS disorders are referenced in the specification, and applicants' invention can be applied to other therapeutic agents as well, whether presently known or discovered in future. For any particular therapeutic agent, the ordinary skilled person can easily prepare and administer conjugates according to the invention that cross the BBB, using the guidance in the specification and techniques known in the art.

The specification shows that Aβ polypeptides can be used to enhance transport of non-Aβ polypeptide therapeutic agents across the blood-brain-barrier (BBB). The specification exemplifies that Aβ polypeptides can be used to transport an anti-amyloid antibody (a species of the genus of non-Aβ polypeptides disclosed in the application) across the BBB better than the antibody

alone. In addition to anti-amyloid antibodies, the specification contemplates the use of various other non-Aβ polypeptides for transport across the BBB for the treatment of various CNS disorders (including Alzheimer's Disease, Parksinson's Disease, fromtotemporal dementias, amyloidotic polyneuropathies, transmissible spongiform encephalopathies, and demyelinating diseases). Exemplary other non-Aβ polypeptides include antioxidant enzymes, interferons, interleukins, neurotrophic factors, neuropoietic factors, growth factor peptides or hormones. See, page 4, lines 8-22.

The specification also teaches how to construct the Aβ polypeptide-non Aβ polypeptide complex recited in the claims. For example, the specification discloses that the Aβ polypeptide and the non-Aβ polypeptide can be linked in a variety of ways, including covalent linkage, non-covalent linkage and specific binding affinity. Thus, applicants have disclosed how to make a composition comprising an Aβ polypeptide and a non-Aβ polypeptide, wherein the Aβ polypeptide and the non-Aβ polypeptide are linked; disclosed various non-Aβ polypeptides; and disclosed how to use the composition to enhance transport of the non-Aβ polypeptides across the BBB for the treatment of various CNS disorders. Accordingly, one of skill in the art would realize from the specification that the Aβ polypeptide-non-Aβ polypeptide transport system could be used to enhance the delivery of a variety of non-Aβ polypeptides at the BBB for the treatment of various CNS disorders. In view of the foregoing, applicants submit that the rejections under 35 U.S.C. § 112, first paragraph (enablement), should be withdrawn.

IV. The rejection under 35 U.S.C. § 102(b) should be withdrawn.

The examiner rejected claims 31, 42-45 and 72 as allegedly being anticipated by Schenk (WO 99/27944), and claims 67-68 as allegedly being anticipated by Solomon et al. (PNAS USA, 94:4109-4112, 1996). Applicants request reconsideration of the rejections in view of the amendments made herein and the following remarks.

Contrary to the examiner's suggestion, Schenk simply does not teach the therapeutic composition comprising a sterile pharmaceutically acceptable carrier or excipient recited in independent claim 31. Notably, Schenk does not disclose or suggest an Aβ polypeptide linked to an agent for the treatment of a CNS disorder (i.e., a therapeutic). According to Schenk, the Aβ polypeptide or analog is used as a vaccine to treat a CNS disorder; thus, any peptide fused to the Aβ polypeptide or analog is not a therapeutic. Anticipation requires that the cited art disclose each and every element of the claims, which is not the case here. Because Schenk fails to teach or suggest an

Aβ polypeptide linked to a non-Aβ polypeptide, wherein the non-Aβ polypeptide is for the treatment of a CNS disorder, Schenk cannot anticipate any of the pending claims. To the extent that the examiner is suggesting that (as in Solomon below) the immune complex between the Aβ polypeptide and the antibody generated by the host's immune response to the vaccination somehow anticipates the claims, applicants disagree because such an immune complex is neither a therapeutic composition nor contains a sterile pharmaceutically acceptable carrier or excipient.

Turning now to the rejection of claim 72, the examiner has not pointed to any part of Schenk which discloses that the composition disclosed therein "exhibits a permeability coefficient x surface area (PS) product of 2.3 x 10-6 ml/g/sec or greater, wherein the PS product is determined after correction for the residual plasma volume (Vp) occupied by the protein in blood vessels in different brain regions following an intravenous bolus injection" as recited in claim 72. Applicants' review of Schenk did not find such a disclosure. Accordingly, Schenk cannot anticipate claim 72. In view of the foregoing, applicants respectfully request that the rejection of claims 31, 42-45 and 72 under 35 U.S.C. §102(b) be withdrawn.

The examiner also rejected claims 67-68 as allegedly being anticipated by Solomon et al. (PNAS USA, 94:4109-4112, 1996). Applicants disagree. Solomon et al. cannot provide the basis for an anticipation rejection for claims 67-68 because Solomon et al. do not teach that the Aβ polypeptide is ***covalently linked*** to a non-Aβ polypeptide. Rather, the Aβ polypeptide is in immunocomplex with an anti-Aβ antibody. It is well known in the art that the interaction between an antibody and its antigen is a ***non-covalent*** linkage (i.e., electrostatic forces, hydrogen bonds, Van der Waals forces or hydrophobic forces). See, for example, Janeway-Travers, Immunobiology, 3rd Ed., page 3-9, set forth in Appendix A. Accordingly, because Solomon et al. do not disclose an Aβ polypeptide that is ***covalently linked*** to a non-Aβ polypeptide, Solomon et al. do not disclose each and every element of claim 67 and therefore cannot destroy the novelty of claim 67 and those claims dependent thereon. In view of the foregoing, applicants respectfully request that the rejection of claims 67-68 under 35 U.S.C. §102(b) be withdrawn.

V. Conclusion

It is believed that the foregoing responds to all of the examiner's concerns. If the examiner believes that a telephone conversation would expedite allowance of the claims, she is invited to contact the undersigned agent or Li-Hsien Rin-Laures, attorney for applicants, at the number below. The Director is hereby authorized to charge any additional fees associated with the filing of this paper to Deposit Account No. 13-2855, under order no. 01017/30016A.

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Respectfully submitted,

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APPENDIX A

3-9 Antigen:antibody interactions involve a variety of forces

The interaction between an antibody and its antigen can be disrupted by high salt concentrations, extremes of pH, detergents, and sometimes by competition by high concentrations of the pure epitope itself. The binding is therefore a reversible non-covalent interaction. The forces, or bonds, involved in these non-covalent interactions are outlined in Fig. 3.10.

The non-covalent forces in antigen:antibody binding can involve electrostatic interactions, either between charged amino acid side chains as in salt bridges, or between electric dipoles as in hydrogen bonds and short-range van der Waals forces. High salt concentrations and extremes of pH disrupt antigen:antibody binding by weakening electrostatic interactions. This principle is employed in purification of antigens by affinity columns of immobilized antibodies or vice versa (see Section 2-7).

Hydrophobic interactions occur when two hydrophobic surfaces come together to exclude water. The strength of hydrophobic interactions is proportional to the surface area that is hidden from water. For some antigens, hydrophobic interactions probably account for most of the binding energy, although this is hard to quantify experimentally.

The contribution of each of these forces to the overall interaction will depend on the specific antibody and antigen involved. A striking difference from other protein–protein interactions is that antibodies possess many aromatic amino acids in their antigen-binding sites; these amino acids participate mainly in van der Waals and hydrophobic interactions, and sometimes hydrogen bonds. Generally speaking the hydrophobic and van der Waals forces operate over very short ranges and serve to pull together two surfaces that are complementary in shape; hills on one surface must fit into valleys on the other for good binding to occur. On the other hand, electrostatic interactions between charged side chains, and hydrogen bonds bridging oxygen and/or nitrogen atoms, accommodate specific features or reactive groups while strengthening the interaction overall. For example, in the complex of hen egg-white lysozyme with the antibody D1.3 (Fig. 3.11), strong hydrogen bonds are formed between the antibody and a particular glutamine in the lysozyme molecule that protrudes between the V_H and V_L domains.

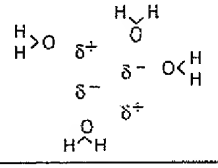
Non-covalent forces	Origin	
Electrostatic forces	Attraction between opposite charges	$-\overset{\oplus}{N}H_3 \quad \overset{\ominus}{O}OC-$
Hydrogen bonds	Hydrogen shared between electronegative atoms (N,O)	$>N-H\cdots O=C<$ $\delta^- \quad \delta^+ \quad \delta^-$
Van der Waals forces	Fluctuations in electron clouds around molecules oppositely polarize neighboring atoms	$\delta^+ \rightleftharpoons \delta^-$ $\delta^- \rightleftharpoons \delta^+$
Hydrophobic forces	Hydrophobic groups interact unfavorably with water and tend to pack together to exclude water molecules. The attraction also involves van der Waals forces	

Fig. 3.10 The non-covalent forces that hold together the antigen–antibody complex. Partial charges found in electric dipoles are shown as δ^+ or δ^-. Electrostatic forces diminish as the inverse square of the distance separating the charges, while van der Waal's forces, which are more numerous in most antigen–antibody contacts, fall off as the sixth power of the separation and therefore operate only over very short ranges. Covalent bonds do not occur between antigens and antibodies.